REMARKS

Entry of the amendments is proper

A response to the Official Action of September 25, 2000 was previously filed on November 21, 2000. The amendments in that response were not entered for a variety of reasons. For example, the Advisory Action of December 4, 2000 stated that the proposed amendments of November 21, 2000 would not be entered because additional claims were presented without cancellation of a corresponding number of finally rejected claims. The present amendment does not include added claims and, therefore, this grounds for non-entry of amendments no longer applies. Furthermore, the present amendment should be entered for at least the following reasons.

A. The Office Action of September 25, 2000 Was Not a Proper Final Rejection

The Office Action of April 14, 2000 included a rejection of claims 1 and 11 under 35 U.S.C. §102(*b*) over Deleersnijder et al (J. Biol. Chem., 271:19475-19482, 1996). Deleersnijder et al, however, was not published more than one year prior to the first effective U.S. filing date of the present application. Therefore, the statutory basis for the rejection over Deleersnijder et al was changed from 35 U.S.C. §102(b) to §102(*a*) by the Action of September 25, 2000. This represents a new ground of rejection which was not necessitated by any amendment introduced by the response filed August 14, 2000. Accordingly, the Office Action of September 25, 2000 cannot properly be issued as a "final rejection," and entry of the present amendments should be made as a matter of right.

B. No New Issues Are Introduced by the Present Amendment

According to the Advisory Action of December 4, 2000, the previous amendment filed November 21, 2000 "raise[d] new issues that would require further consideration and/or search." The present amendment merely revises claim 1 to recite that a biologically active or immogenic fragment "comprising at least 15 contiguous amino acids" of an amino acid sequence of SEQ ID NO:1. The issue of fragments ***comprising at least 15 contiguous amino acids*** of SEQ ID NO:1 was squarely addressed regarding the rejection over Deleersnijder et al on page 21 of the response filed November

21, 2000. Furthermore, the comments on page 7 of the Office Action show that the Examiner considered this feature. Moreover, paragraph 4 of the Advisory Action states that entry of the amendment to claim 1 would overcome the §102(a) rejection over Deleersnijder et al. Clearly, then, entry of the amendment to claim 1 would not "raise new issues."

C. Entry of the Amendment to Claim 1 Would Reduce Issues for Appeal

Even if the subject application was not now allowed, entry of the amendment to claim 1 would reduce issues for appeal. As discussed above, paragraph 4 of the Advisory Action of December 4, 2000 expressly states that entry of the amendment to claim 1 would overcome the rejection based on Deleersnijder et al. Accordingly, the present should be entered.

D. The Patent Office Desires to Issue Patents as Quickly as Possible

This is the era of the "caring and sharing" Patent Office of the new millennium. The Patent Office has indicated a desire to serve its customers by providing the best possible service, including the quick issuance of patents. Certainly the use of gamesmanship by Patent Office employees via strained and onerous interpretation of Patent Office rules does not fit into the mission of providing beneficial customer service. Hence, entry of the presently proposed amendments would best serve the goals of the Patent Office, either by resulting in the immediate allowance of the subject application or by the expeditious facilitation of an appeal.

For at least the above reasons, entry of the amendments to claim 1 is believed to be in order.

Rejections for lack of utility under 35 U.S.C. §101 and §112

With respect to the "utility rejections" under 35 U.S.C. §§ 101 and 112, first paragraph, Applicants traverse the rejections again, reiterating their previous remarks. Applicants note that the Examiner's "Response to Arguments" not only ignores the substance of Applicants' legal arguments ("Applicants assert that the Guidelines are themselves inconsistent with the law at pages 8-21. The Examiner will only address parts of this critique as it applies to the instant invention and rejection."), it

also ignores Applicants' fully developed arguments, supported by sound reasoning and references showing same, regarding the very real-world, substantial, specific and credible utility of toxicology testing. Applicants in particular note that this utility is **specific** to detection of the claimed sequences (the claimed sequences will hybridize to only the same or almost identical sequences, not all sequences), is **substantial** in that it is a crucial part of many if not all drug development process used by pharmaceutical companies and thus has enormous public benefit, and it is certainly is **credible** to one of ordinary skill in the art (lack of credibility was not asserted in the Office Action).

It is clear that Applicants have not only disclosed in the specification a specific, substantial and credible utility, they have also established that it is a well-known utility have a very real-world application which is, in its presently available form, providing a substantial public benefit.

Written description rejection under 35 U.S.C. §112, first paragraph

Claims 1 and 11 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every

> nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification provides an adequate written description of the claimed biologically active fragments and immunogenic fragments of SEQ ID NO:1

The Office Action has asserted that the Specification does not provide an adequate written description of the claimed biologically active fragments and immunogenic fragments of SEQ ID NO:1. Such, however, is not the case

At pages 13-15, the Specification describes the polynucleotide of SEQ ID NO:2 and the polypeptide encoded by that polynucleotide, *i.e.*, SEQ ID NO:1, and chemical and structural characteristics thereof. The polypeptide and fragments thereof can be produced by either recombinant means (see, *e.g.*, the Specification at pages 16-27) or by chemical synthesis (see, *e.g.*, the Specification at page 20, lines 13-20; and page 27, lines 17-23). Polynucleotides can also be synthesized by chemical methods (see, *e.g.*, the specification at page 20, lines 13-15).

Note that at page 8, lines 11-12, biologically active is defined as "a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule" and immunologically active" is defined as "the capability of the natural, recombinant, or synthetic IMP-2, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies." Specific binding is further defined at page 12 as meaning that:

> . . . in reference to the interaction of an antibody and a protein or peptide, mean[s] that the interaction is dependent upon the presence of a particular structure (i.e., the antigenic determinant or epitope) on the protein; in other words, the antibody is recognizing and binding to a specific protein structure rather than to proteins in general. For example, if an antibody is specific for epitope "A", the presence of a protein containing epitope A (or free, unlabeled A) in a reaction containing labeled "A" and the antibody will reduce the amount of labeled A bound to the antibody.

Methods of producing specifically binding antibodies are described, for example, at pages 29-30. In this regard, note page 29, lines 19-25 which describes fragment sizes of IMP-2 (i.e., SEQ ID

NO:1) for raising antibodies. See also page 51 which describes the production of antibodies to fragments of IMP-2, including the description of how to identify appropriate immunogenic sites of IMP-2:

> The amino acid sequence deduced from SEQ ID NO:2 is analyzed using DNASTAR software (DNASTAR Inc) to determine regions of high immunogenicity, and a corresponding oligopolypeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions, is described by Ausubel et al. (supra), and others. (Specification at page 51, lines 13-17)

Furthermore, the Specification describes at page 50, line 4 to page 51, line 8, methods for demonstrating biological activity of IMP-2 proteins.

Given the "blueprint" provided by SEQ ID NO:1, and the detailed guidance set forth by the Specification, the structure of fragments of SEQ ID NO:1 is apparent and there is no need to explicitly list the sequences of the numerous possible fragments. Such a list would just needlessly clutter the Specification.

B. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1

The Office Action further asserts that "[t]he specification does not teach naturally occurring amino acid sequences having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:1. Therefore, one skilled in the art would not know what this naturally occurring sequence would look like, or if the sequence represents a functional protein." However, the subject matter encompassed by the claims is either disclosed by the Specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 1 recites a polypeptide comprising "a naturally-occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:1."

The amino acid sequence of SEQ ID NO:1 is explicitly disclosed in the Specification. See, for example, Figure 1. One of skill in the art would know how to provide polynucleotide sequences encoding SEQ ID NO:1 as well as complements thereof. In this regard, the Specification also explicitly discloses the particular polynucleotide species of SEQ ID NO:2, which encode the amino acid sequence of SEQ ID NO:1 (see Figure 1). Similarly, one of skill in the art would recognize polynucleotide sequences encoding

variants of SEQ ID NO:1. The Specification further describes, *e.g.*, at page 15, lines 24-27, naturally-occurring polypeptide variants of IMP-2 (i.e., SEQ ID NO:1). Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are relevant to "protein claims" by virtue of the capability of DNA to encode protein) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of functional features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant phasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides in terms of chemical structure, rather than on functional characteristics. As discussed above, the "variant language" of independent claim 1 recites chemical structure to define the claimed genus:

> 1. A substantially purified polypeptide comprising . . . b) a naturally-occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:1 . . .

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the claimed polypeptides. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the claimed polypeptides. The polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims to nucleic acids and polypeptides. By failing to base its written description inquiry "on whatever

is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that, rather than being highly variant, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to integral membrane proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as integral membrane proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 266 amino acid residues). This variation is far less than that of all potential integral membrane proteins related to SEQ ID NO:1, i.e., those integral membrane proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

The case of *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) provides further support for concluding that the polypeptide genus defined by the present claims complies with the written description requirement. As discussed above, certain claims of U.S. Patent No. 4,652,525 were found invalid for failing to satisfy the written description requirement. The *Lilly*

case, however, also considered U.S. Patent No. 4,431,740. While there is a discussion in *Lilly* of issues of infringement and enforceability of the claims of the '740 patent, there is no written description analysis of the claims of the '740 patent. However, there was no holding of invalidity of any claim of the '740 patent. Thus, the claims of the '740 patent are presumed to satisfy the written description of 35 U.S.C. §112. See 35 U.S.C. §282. Now consider, for example, claim 4 of the '740 patent, which reads as follows:

> 4. A DNA transfer vector comprising a deoxynucleotide sequence coding for human pre-proinsulin consisting essentially of a plus strand having the sequence:

5'-$_{-24}$ GCL$_{-23}$ X$_{22}$ TY$_{-22}$ TGG$_{-21}$ ATG$_{-20}$ W$_{-19}$ GZ$_{-19}$ X$_{-18}$ TY$_{-18}$ X$_{-17}$ TY$_{-17}$ CCL$_{-16}$ X$_{-15}$TY$_{-15}$ X$_{-14}$ TY$_{-14}$ GCL$_{-13}$ X$_{-12}$ TY$_{-12}$ X$_{-11}$ TY$_{-11}$ GCL$_{-10}$ X$_{-9}$ TY$_{-9}$ TGG$_{-8}$ GGL$_{-7}$ CCL$_{-6}$GAK$_{-5}$ CCL$_{-4}$ GCL$_{-3}$ GCL$_{-2}$ GCL$_{-1}$ TTK$_1$ GTL$_2$ AAK$_3$ CAJ$_4$ CAK$_5$ X$_6$ TY$_6$ TGK$_7$ GGL$_8$ QR$_9$ S$_9$ CAK$_{10}$ X$_{11}$ TY$_{11}$ GTL$_{12}$ GAJ$_{13}$ GCL$_{14}$ X$_{15}$ TY$_{15}$ TAK$_{16}$ X$_{17}$ TY$_{17}$ GTL$_{18}$ TGK$_{19}$ GCL$_{20}$ GAJ$_{21}$ W$_{22}$ GZ$_{22}$ GCL$_{23}$ TTK$_{24}$ TTK$_{25}$ TAK$_{26}$ ACL$_{27}$ CCL$_{28}$ AAJ$_{29}$ ACL$_{30}$ W$_{31}$ GZ$_{31}$ W$_{32}$ GZ$_{32}$ GAJ$_{33}$ GCL$_{34}$ GAJ$_{35}$ GAK$_{36}$ X$_{37}$ TY$_{37}$ CAJ$_{38}$ GTL$_{39}$ GGL$_{40}$ CAJ$_{41}$ GTL$_{42}$ GAJ$_{43}$ X$_{44}$ TY$_{44}$ GGL$_{45}$ GGL$_{46}$ GGL$_{47}$ CCL$_{48}$ GGL$_{49}$ GCL$_{50}$ GGL$_{51}$ QR$_{52}$ S$_{52}$ X$_{53}$ TY$_{53}$ CAJ$_{54}$ CCL$_{55}$ X$_{56}$ TY$_{56}$ GCL$_{57}$ X$_{58}$ TY$_{58}$ GAJ$_{59}$ GGL$_{60}$ QR$_{61}$ S$_{61}$ X$_{62}$ TY$_{62}$ CAJ$_{63}$ AAJ$_{64}$ W$_{65}$ GZ$_{65}$ GGL$_{66}$ ATM$_{67}$ GTL$_{68}$ GAJ$_{69}$ CAJ$_{70}$ TGK$_{71}$ TGK$_{72}$ ACL$_{73}$ QR$_{74}$ S$_{74}$ ATM$_{75}$ TGK$_{76}$ QR$_{77}$ S$_{77}$ X$_{78}$ TY$_{78}$ TAK$_{79}$ CAJ$_{80}$ X$_{81}$ TY$_{81}$ GAJ$_{82}$ AAK$_{83}$ TAK$_{84}$ TGK$_{85}$ AAK$_{86}$ TAGACGCAGCCCGCAGGCAGCCCCCCACCCGCCGCCTCCTGCACCGAGAGAGATGGA ATAAAGCCCTTGAACCA GC polyA-3'

> wherein
>
> A is deoxyadenyl,
>
> G is deoxyguanyl,
>
> C is deoxycytosyl,
>
> T is thymidyl,
>
> J is A or G;
>
> K is T or C;
>
> L is A, T, C, or G;
>
> M is A, C or T;
>
> X_n is T or C if Y_n is A or G; and C if Y_n is C or T;

Y_n is A, G, C or T if X_n is C, and A or G if X_n is T;

W_n is C or A if Z_n is G or A, and C if Z_n is C or T;

Z_n is A, G, C or T if W_n is C, and A or G if W_n is A;

QR_n is TC if S_n is A, G, C or T, and AG if S_n is T or C;

S_n is A, G, C or T if QR_n is TC, and T or C if QR_n is AG; and, script numerals, n, refer to the position in the amino acid sequence of human proinsulin, to which each triplet in the nucleotide sequence corresponds, according to the genetic code, the amino acid positions being numbered from the amino end.

Claim 4 of the '740 patent recites a DNA sequence with includes the coding region for human pre-proinsulin; in particular, the 330 nucleotide bases from codon GCL_{-23} through codon AAK_{86} code for human pre-proinsulin. As can be seen from the claim language, claim 4 of the '740 patent sets forth a DNA structure with numerous variant positions. Of the 330 nucleotides in the coding region for human pre-proinsulin, 141 are potentially variant positions within the structure defined by claim 4. Thus, claim 4 of the '740 patent defines a DNA which potentially is only 57% identical (189/330 x 100% = 57%) to the single species of human pre-proinsulin actually sequenced in the '740 patent. See Example 1 and Figure 2. As discussed above, the present claims encompass naturally-occurring polypeptide variants which have at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1. Clearly, then, the genus variation of the present claims is less than that of claim 4 of the '740 patent.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of January 31, 1997. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the ject application, the present inventors were in possession of the claimed polypeptide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to polypeptides and nucleic acids. In addition, the genus of polypeptides defined by the present claims is not "highly variant," as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the Specification provides an adequate written description of the claimed subject matter, and withdrawal of this rejection is therefore requested.

Rejection under 35 U.S.C. §102(a)

As indicated by paragraph 4 of the Advisory Action, the amendments to claim 1 obviate the rejection based on Deleersnijder et al. Withdrawal of this rejection is therefore requested.

CONCLUSION

For at least the above reasons, it is submitted that the present application is fully in condition for allowance, and withdrawal of the outstanding rejections is requested. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, the Examiner is invited to contact the undersigned attorney.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,

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Date: 22 February 2001

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